SCIENTIFIC ABSTRACT (Introductory statement and general investigational plan)

Concept summary:

This is a phase 1 dose finding and toxicity study in which patients with recurrent malignant glioblastoma are treated with adenovirus vector containing the herpes simplex thymidine kinase gene (ADV-tk). The tumor tissue visible on contrast enhanced MRI scan will be resected prior to ADV-tk administration. Frameless stereotactic surgical technique will be used to remove the maximal amount of tumor tissue. Then the ADV-tk will be injected into the margins of the tumor cavity. This treatment design minimizes the distance which ADV-tk must penetrate to reach the tumor cells infiltrating into the brain tissue surrounding the tumor mass. Beginning 24 hours after the injection of the ADV-tk the patients receive intravenous ganciclovir (10mg/kg/day in two divided daily doses) for seven days. The initial dose of ADV-tk will be $1.0x\ 10^7$pfu and 3 patients will be treated at this dose. If no grade 3 or 4 neurologic or systemic toxicity is observed, the dose of ADV-tk will be escalated in 0.5 log increments as mandated by the FDA for similar human trials involving viral vectors. Three patients will be studied at each dose level. If any of 3 patients develop grade 3 or 4 neurologic or systemic toxicity, then 2 more patients will be entered at that dose. If 3 of 5 patients at a given dose develop grade 3 or 4 toxicity, the dose excalation will be terminated, and the dose one increment below that dose will be considered the maximum tolerated dose of ADV-tk. If 2 of 5 patients develop grade 3 or 4 toxicity at a given dose, then dose escalation will proceed at 0.25 log intervals until 3 of 5 patients in a dosing group develop grade 3 or 4 toxicity, at which time the escalation will be terminated and the dose level one increment lower than the final dose level will be the MTD.

We will monitor toxicity by serial neurologic examinations, laboratory tests to detect systemic toxicity related to the ADV-tk or ganciclovir, and radiologically with serial MRI scans of the brain beginning immediately after viral injection and continuing for 2 years post treatment to identify potential late complications of the therapy. Although efficacy can not be evaluated in this phase 1 study, the interval to progression of disease by clinical and radiologic criteria will be monitored in these patients.